Response to Symptom-Limited Exercise in Patients With the Hepatopulmonary Syndrome*

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**Objective:** To study the response to symptom-limited exercise in patients with the hepatopulmonary syndrome (HPS).

**Design:** The response to maximal cardiopulmonary exercise (CPX) was studied in 5 patients with HPS and compared with 10 case control (normoxemic, NC) cirrhotics (matched for age, gender, etiology and severity of liver disease, tobacco use, and β-blocker therapy) and 9 hypoxemic control cirrhotics (HC) without clinical evidence of HPS.

**Setting:** Cardiopulmonary exercise physiology laboratory in a tertiary care referral center.

**Patients:** Cirrhotics referred for CPX as part of their preliver transplantation evaluation.

**Measurements:** Standard pulmonary function tests and echocardiography were performed to assess resting pulmonary and cardiac function. Peak oxygen consumption (Vo2), minute ventilation, arterial blood gases, and dead space (Vd/Vt) were determined during symptom-limited maximal CPX.

**Results:** Resting spirometry and lung volumes were similar between HPS and NC subjects, while HC subjects had restrictive physiology. Differences existed in diffusion capacity corrected for hemoglobin and alveolar volume percent predicted (HPS, 45±2 vs NC, 68±3, p<0.05; vs HC, 70±4, p<0.05), PaO2 (HPS, 70±5 mm Hg; HC, 79±3 mm Hg; vs NC, 102±3 mm Hg, p<0.05) and alveolar-arterial (A-a) O2 gradient (HPS, 42±8 mm Hg vs HC, 27±2 mm Hg, p<0.05; vs NC, 6±2 mm Hg, p<0.05). During CPX, HPS patients achieved a lower peak Vo2 percent predicted (HPS, 55±6 vs NC, 73±3, p<0.05; vs HC, 71±5, p<0.05) and Vo2 at the ventilatory threshold as percent predicted peak Vo2 (HPS, 36±2 vs NC, 55±4, p<0.05; vs HC 55±5, p<0.05). While no differences existed in heart rate and breathing reserve, HPS patients had significantly lower PaO2 (HPS, 50±5 mm Hg vs NC, 97±4 mm Hg, p<0.05; vs HC, 87±6 mm Hg, p<0.05), wider A-a O2 gradient (HPS, 73±5 mm Hg vs NC, 13±3 mm Hg, p<0.05; vs HC, 31±5 mm Hg, p<0.05) and higher Vd/Vt (HPS, 0.36±0.03 vs NC, 0.18±0.02, p<0.05; vs HC, 0.28±0.02, p<0.05) at peak exercise. For HPS patients, Vo2 was negatively correlated with Vd/Vt (r2=0.9) and positively correlated with PaO2 (r2=0.41) at peak exercise.

**Conclusions:** Patients with HPS demonstrate a severe reduction in aerobic capacity, beyond that found in cirrhotics without syndrome. The significant hypoxemia and elevated Vd/Vt at peak exercise suggest that an abnormal pulmonary circulation contributes to further exercise limitation in patients with HPS.

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**Key words:** cirrhosis; exercise testing; gas exchange; hepatopulmonary syndrome; pulmonary vascular disease

**Abbreviations:** A-a O2=alveolar-arterial oxygen; CPX=cardiopulmonary exercise testing; DCOcorrVo2=diffusing capacity corrected for hemoglobin and alveolar volume; HC=normoxemic control subjects; HPS=hepatopulmonary syndrome; HR=heart rate; MVV=maximal voluntary ventilation; NC=normoxemic control subjects; TLC=total lung capacity; Vd/Vt=dead space; VE=minute ventilation; Vo2=oxygen consumption; V/Q=ventilation/perfusion ratio

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The triad of severe liver dysfunction (usually cirrhosis), gas exchange abnormalities (widened alveolar-arterial oxygen [A-a O2] gradient and hypoxemia), and evidence of intrapulmonary vascular dilatation, in the absence of other cardiopulmonary disease, has been termed the hepatopulmonary syndrome (HPS).1,2 Approximately 20% of patients present with shortness of breath and the course of disease is characterized by progressively increasing dyspnea, effort intolerance, and worsening hypoxemia.3 Agusti et al4 have provided elegant physiologic descriptions of the gas exchange abnormalities during exercise in cirrhotics with mild hypoxemia. In contrast, studies of cardiopulmonary exercise in pa-
patients fulfilling the criteria for HPS, and with more significant resting hypoxemia, have been confined to case reports and small, uncontrolled series.

These isolated descriptions provide limited information on the impact of HPS on exercise capacity because cirrhosis alone (in the absence of clinical manifestations of the HPS) is associated with significant exercise impairment. Therefore, we investigated the response to maximal cardiopulmonary exercise testing (CPX) in five patients with established HPS and compared this to both normoxic and hypoxicemic cirrhotics without clinical evidence of the syndrome.

**Materials and Methods**

**Study Patients**

The study population consisted of five patients, referred for CPX as part of the preliver transplant assessment, who had a diagnosis of HPS based on the presence of cirrhosis, resting hypoxemia with a widened A-a O2 gradient ($\geq$20 mm Hg), and a positive contrast-enhanced two-dimensional transthoracic echocardiogram. Because cardiopulmonary exercise abnormalities are frequently present in patients with cirrhosis in the absence of HPS, we carried out a case-control study. In blinded fashion, two control subjects (normoxic control subjects, NC) were matched for each study patient based on age ($\pm$5 years), gender, etiology of cirrhosis, severity of liver disease based on the Childs-Pugh classification ($\pm$1 point on the Pugh score), history of tobacco use, and treatment with nonselective $\beta$-blockade. In addition, control patients were required to have no clinical evidence of HPS, including absence of clubbing, cyanosis, platypnea, orthodeoxia, hypoxemia (eg, PaO2 <90 mm Hg or A-a O2 gradient $\geq$20 mm Hg), or severe reduction in diffusing capacity corrected for hemoglobin and alveolar volume (DCOcorr/VA $\leq$50% predicted). Because resting hypoxemia is the principal pathophysiological manifestation of HPS, we also wanted to compare the exercise response to that of cirrhotics with resting hypoxemia unrelated to HPS. Therefore, we also identified nine patients with cirrhosis (hypoxic control subjects, HC) who had both PaO2 <90 mm Hg and A-a O2 gradient $\geq$20 mm Hg in the absence of any of the following: severe hypoxemia (PaO2 <70 mm Hg); other clinical manifestations of HPS (clubbing, platypnea, orthodeoxia, or DCOcorr/VA $\leq$50% predicted); history or radiographic evidence of obstructive lung disease, interstitial lung disease, pulmonary hypertension, or hepatic hydrothorax (large unilateral pleural effusion occupying more than one-fourth of the hemithorax). These patients all had at least moderate ascites and three had pleural effusions occupying less than one-fourth of a hemithorax.

**Preexercise Protocol**

Standard resting pulmonary function testing consisted of spirometry (FEV1, FVC, and the FEV1/FVC ratio), static lung volumes (total lung capacity, TLC) determined using either the nitrogen washout or helium dilution methods, and DCOcorr/VA. Arterial blood gases were obtained, with patients in the upright position, by either radial or brachial artery puncture. Resting cardiac function was measured by two-dimensional transthoracic echocardiography with the left ventricular ejection fraction calculated by visual inspection. Contrast echocardiography was performed by injecting microbubbles, generated from agitated normal saline solution, into a peripheral venous catheter. A study was considered positive if "contrast" appeared in the left atrium three to six cardiac cycles after being detected in the right heart chamber.

**Exercise Protocol**

Symptom-limited CPX was performed on a cycle ergometer using a continuous ramp protocol with work rate increasing by 10 to 15 W/min after a 1-min unloaded warm-up period. All patients were studied in the upright position and were monitored continuously with pulse oximetry and 12-lead ECG to determine heart rate (HR). Oxygen uptake (VO2), carbon dioxide production, minute ventilation (VE), respiratory rate, and tidal volume (VT) were determined using a metabolic cart. The oxygen pulse (VO2/HR) was calculated by dividing the VO2 by the HR. Peak metabolic and ventilatory values were determined by averaging all breaths in the final 15 s of exercise. A catheter was positioned in either the brachial or radial artery in all HPS patients, all HC subjects, and in nine NC subjects. Arterial blood gases and lactate levels were measured at rest and at peak exercise. All studies were conducted on room air (fraction of inspired oxygen=0.21). Predicted values for work rate and peak VO2 were calculated using published equations. Predicted peak HR was determined using the equation, 220-age. Predicted peak breathing capacity was determined using the 12-s maximal voluntary ventilation (MVV) maneuver. Breathing reserve (as a percentage) was then calculated as equal to the (MVV-peak VE)/MVV. Dead space was determined using the equation, Vd/VT=[(PaCO2-PaECO2)/PaCO2-Vd(machine)/VT], where Vd/VT is the dead space, PaECO2 is the partial pressure of mixed expired CO2, and Vd(machine)/VT is the mechanical dead space of the apparatus. The ventilatory (anaerobic) threshold (VT) was determined using the gas exchange method (V slope). For each patient, VT was determined by a consensus of at least two of the investigators blinded to group assignment. All patients gave informed consent for the exercise protocol approved by the institution.

**Statistical Analysis**

Mean values ($\pm$SEM) were computed for all recorded parameters. A $\chi^2$ with a two-tailed Fisher's Exact Test for noncontinuous variables was used to compare the groups. A Student's t test was used to compare resting values with peak exercise values. A one-way analysis of variance was used to assess the significance of group differences. Post hoc analysis (Student-Newman-Keuls test) was performed to adjust for multiple comparisons. When Levene's test suggested unequal variances, a nonparametric test (Kruskal Wallis H) was used to compare group means. If appropriate, a Mann-Whitney U test was performed to further compare group differences. Correlation analysis was performed to further examine the relationship between peak VO2 (percent predicted) and peak exercise measurements of gas exchange. Software (SPSS version 6.1; Chicago [1994]) was used for statistical analysis.

**Results**

The five HPS patients consisted of four men and one woman with ages ranging from 38 to 50 years old. Cirrhosis had been present for 65±16 months (range, 24 to 120 months) and was etiologically...
related to hepatitis C (three patients), hepatitis C and alcohol (one), and alcohol (one). The diagnosis of HPS was originally entertained because of one or more of the following: platypneaa/orhodoxia (three patients), clubbing (three), severe resting hypoxemia or PaO₂ <70 mm Hg (three), unexplained dyspnea (four), or severe reduction in diffusion capacity (D̄co2corr/VA ≤50% predicted) on resting pulmonary function tests (five). Four HPS patients had a history of smoking and one was taking a β-blocker. Mild ascites was present in three HPS patients and in six NC subjects. With the exception of prominent pulmonary vascular markings at the bases (two patients), the chest radiograph was otherwise normal in all HPS patients. Three control subjects (two NC, one HC) had an abnormal chest radiograph consisting of platelike atelectasis. Baseline clinical features were similar between HPS patients and control subjects except for a lower serum albumin level in the former (Table 1). The HC subjects were significantly older than the other cirrhatics. Among the HC subjects, there were five women and four men; four patients had a history of smoking and the following distribution of liver disease was present: primary biliary cirrhosis (two), primary sclerosing cholangitis (one), hepatitis C (three), alcoholic (one), hepatitis B (one), and autoimmune (two).

There was no difference between the HPS patients and the NC subjects in resting spirometry and lung volumes (Table 2). The HC subjects had restrictive physiology with lower values for FEV₁ percent predicted, FVC percent predicted, and TLC percent predicted. The D̄co2corr/VA was significantly reduced in the HPS patients (range, 38 to 50% predicted). Although the D̄co2corr (as percent predicted) was significantly reduced in the HC compared with the NC subjects, in contrast to HPS, this increased substantially when corrected for alveolar volume. The HPS patients had a higher resting respiratory rate and Vt than the NC subjects, though these did not reach statistical significance. The HC subjects had a higher respiratory rate compared with NC subjects and a lower Vt compared with both groups. In comparison to NC subjects, the HPS patients and HC subjects had significant resting hypoxemia with a widened A-a O₂ gradient and alkalemia (Table 3). The HPS patients tended toward a lower resting PaCO₂ when compared with control subjects. The groups were similar in resting left ventricular ejection fraction, HR, V̇O₂, and serum lactate levels (Table 3). Neither right ventricular systolic dysfunction nor elevated pulmonary artery systolic pressures were identified in any of the 24 patients studied.

Table 2—Resting Pulmonary Function*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HPS</th>
<th>NC</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, % pred</td>
<td>90±4</td>
<td>91±3</td>
<td>73±6*</td>
</tr>
<tr>
<td>FVC, % pred</td>
<td>98±4</td>
<td>105±2</td>
<td>79±6*</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>75±3</td>
<td>72±2</td>
<td>73±4</td>
</tr>
<tr>
<td>FEF25-75, % pred</td>
<td>71±5</td>
<td>61±9</td>
<td>53±8</td>
</tr>
<tr>
<td>TLC, % pred</td>
<td>96±3</td>
<td>92±3</td>
<td>74±6*</td>
</tr>
<tr>
<td>D̄co2corr, % pred</td>
<td>43±2</td>
<td>73±4</td>
<td>54±4*</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>16±2</td>
<td>13±1</td>
<td>17±2</td>
</tr>
<tr>
<td>Vt, mL</td>
<td>0.98±0.12</td>
<td>0.97±0.11</td>
<td>0.71±0.07</td>
</tr>
<tr>
<td>V̇E, L/minute</td>
<td>15.8±2.7</td>
<td>11.9±0.8</td>
<td>12.1±1.1</td>
</tr>
</tbody>
</table>

*FEF25-75=forced expiratory flow rate between 25% and 75% of the FVC; pred=predicted.

Table 3—Resting Gas Exchange, Metabolic, and Cardiac Function Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HPS</th>
<th>NC</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂, mm Hg</td>
<td>70±5</td>
<td>102±3*</td>
<td>79±3*</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>31±3</td>
<td>35±1</td>
<td>35±2</td>
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<tr>
<td>pHa</td>
<td>7.44±0.01</td>
<td>7.41±0.01</td>
<td>7.46±0.01*</td>
</tr>
<tr>
<td>A-a O₂ gradient, mm Hg</td>
<td>42±5</td>
<td>6±2*</td>
<td>27±2*</td>
</tr>
<tr>
<td>V̇O₂/HR</td>
<td>0.37±0.03</td>
<td>0.33±0.02</td>
<td>0.40±0.01*</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>63±1</td>
<td>64±4</td>
<td>63±1</td>
</tr>
<tr>
<td>V̇O₂, mL/kg/min</td>
<td>3.6±0.6</td>
<td>3.5±0.1</td>
<td>3.3±0.3</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>88±8</td>
<td>76±4</td>
<td>81±5</td>
</tr>
<tr>
<td>Lactate, mEq/L</td>
<td>1.2±0.1</td>
<td>1.0±0.1</td>
<td>1.3±0.2</td>
</tr>
</tbody>
</table>

*p<0.05, HPS patients compared with NC subjects.

†p<0.05, HPS patients compared with HC subjects.

‡p<0.05, NC subjects compared with HC subjects.

§pHα=arterial pH.
patients compared with 55% in the control subjects. Although the HPS patients had a higher peak respiratory rate and a higher peak VE, there was no evidence of pulmonary mechanical limitation using breathing reserve or tidal volume to inspiratory capacity ratio criteria.  

At peak exercise, all five HPS patients had a reduction in PaO₂ resulting in severe hypoxemia (PaO₂ range 41 to 66 mm Hg; mean decrease in PaO₂=20 mm Hg, range 12 to 25 mm Hg, p<0.01). The PaO₂ decreased in five of nine NC subjects with exercise, but the magnitude was small and not statistically significant (PaO₂ range 86 to 115 mm Hg; mean decrease in PaO₂=2 mm Hg, range 20 mm Hg increase to 23 mm Hg decrease). Conversely, the PaO₂ further decreased in three of nine HC subjects and overall, there was a trend toward an increase in PaO₂ at peak exercise (PaO₂ range 62 to 111 mm Hg; mean increase 7 mm Hg; range 11 mm Hg decrease to 27 mm Hg increase). The PaO₂ at peak exercise was positively correlated with peak VO₂ (percent predicted) in the HPS group (r²=0.41), but not in the control subjects (NC, r²=0.03; HC, r²=0.08). The A-a O₂ gradient widened during exercise in all HPS patients (A-a O₂ gradient range 60 to 86 mm Hg; mean increase in A-a O₂ gradient=13 mm Hg, range 11 mm Hg increase to 23 mm Hg decrease.  

The principal findings of this study are that, when compared with control cirrhotics (with and without hypoxemia), patients with HPS and significant resting hypoxemia demonstrate severe reductions in exercise capacity and peak VO₂, characterized by worsening hypoxemia, early onset of the ventilatory threshold, and elevated Vd/Vt at peak exercise. By studying patients satisfying the definition of HPS during symptom-limited CPX and comparing these with control cirrhotics without clinical evidence for HPS, this investigation differs significantly from previous reports.

Hypoxemia with a widened A-a O₂ gradient is frequently present in patients with cirrhosis, but Krowka et al have shown that only a minority have intrapulmonary vascular dilatations by contrast echocardiography. With normoxemia or mild-moderate hypoxemia, studies using the multiple inert gas technique demonstrate only mild-moderate ventilation/perfusion (V/Q) inequality, without significant shunt or diffusion limitation. With proven or probable HPS, worsening V/Q mismatch and increasing shunt and diffusion impairment are present. The term perfusion-diffusion defect has been used because, unlike true anatomic shunt, most patients have a substantial improvement in PaO₂.
with 100% oxygen. In addition, hemodynamic studies of patients with probable or definite HPS demonstrate decreased pulmonary vascular resistance, reduced hypoxic vasoconstriction, and diminished response to almitrine, all consistent with resting pulmonary vascular dysfunction. Agusti et al, studying six normoxic cirrhotics (mean PaO2, 99 mm Hg; A-a O2, 15 mm Hg) before and during steady-state submaximal exercise, found no change in V/Q mismatch, minimal shunt, or limitation in oxygen diffusion. As with our NC group, these authors noted exercise-related decreases in PaO2 and increases in A-a O2 gradient, though present in the majority, were small in magnitude. Thus, in the absence of resting hypoxemia, exercise minimally affects gas exchange in cirrhotics without clinical evidence of the HPS. In contrast, our HC subjects actually demonstrated a trend toward a slightly higher PaO2 with exercise. Based on our exclusion criteria in selecting these patients, we believe that hypoxemia principally resulted from compressive atelectasis resulting from ascites or pleural fluid. These processes would explain the finding of restrictive physiology and substantial improvement in DCo2corr/VA seen in this group. With the increasing Vt values seen with exercise, ventilation to atelectic areas may improve, resulting in less V/Q mismatch and an increase in PaO2. Similar observations have been made in patients with compressive atelectasis resulting from obesity.

Several investigators have demonstrated reduced exercise capacity in patients with cirrhosis, but to our knowledge, systematic studies of the effect of HPS on maximal exercise capacity have not been reported. In agreement with previous case reports and small, uncontrolled series, we found significant exercise-related hypoxemia in patients with HPS. The worsening hypoxemia during exercise in HPS may result from one or more mechanisms. In patients with only mild resting hypoxemia and V/Q mismatch, the capacity to increase cardiac output during exercise may minimize the fall in PaO2 through effects on mixed venous oxygen tension. This may not be the case in HPS when significant shunt and diffusion abnormality are also present. The increased cardiac output during exercise reduces pulmonary circulation transit time, amplifying the perfusion-diffusion defect by disrupting the equilibration of alveolar and capillary Po2. In addition, the increased pulmonary blood flow may preferentially course through intrapulmonary vascular dilatations (areas of very low V/Q) amplifying their effect, eg, worsening V/Q mismatch. This would also be the case if other areas of the pulmonary circulation were unable to accept the increased pulmonary blood flow. These mechanisms are supported by the finding that, unlike control cirrhotics, patients with HPS fail to normally decrease Vd/Vt at peak exercise, indicative of an abnormal pulmonary vascular response to exercise or worsening V/Q mismatch. In an uncontrolled study, Wolfe et al made similar observations in three patients, noting an increase in Vd/Vt from 0.31 to 0.36 and an abnormal increase in pulmonary vascular resistance during symptom-limited exercise. Agusti et al proposed the concept of a maximally dilated pulmonary circulation and reduced pulmonary vascular reserve when they found that pulmonary vascular resistance failed to decrease appropriately with exercise in mildly hypoxic cirrhotics. Lastly, with increasing muscular exercise, peripheral oxygen extraction will increase, reducing the mixed venous oxygen content (already lowered by the effect of hypoxemia and decreased arterial oxygen content), further amplifying the effect of the perfusion-diffusion abnormality.

A number of causes for reduced maximal exercise capacity and peak VO2 in cirrhosis have been postulated, including an abnormal chronotropic or inotropic response to exercise (cirrhotic cardiomyopathy), musculoskeletal disease (cirrhotic myopathy), and abnormal peripheral oxygen extraction. In comparing cirrhotics with and without HPS, we found no statistical difference in HR response or pulmonary mechanical limitation, though the former group had significantly lower peak VO2 (percent predicted) and Vo2 at the ventilatory threshold (as percent predicted peak VO2). In contrast, marked differences in gas exchange were identified, with the HPS patients having significantly lower PaO2 and higher Vd/Vt at peak exercise. Importantly, HPS patients demonstrated stronger correlations between VO2 (percent predicted) and PaO2 and Vd/Vt at peak exercise, respectively. Taken together, these findings suggest that the abnormal pulmonary vascular function seen with HPS contributes, in part, to exercise limitation.

There are several potential limitations to our study. First, we studied a select group of ambulatory patients, undergoing elective evaluation for liver transplantation and capable of undergoing CPX. Second, because relatively few patients with hypoxemia without clinical HPS were identified, we were unable to control for age, gender, and etiology of liver disease. The impact of these factors should be minimized by the use of age-gender-derived predicted values and by the similarity of severity of liver disease based on the pugh score. Third, the control groups did not undergo contrast echocardiography, making it possible that some had intrapulmonary vascular dilatations in the absence of clinical evidence of HPS. This should not detract from our analysis because the intent was to examine the exercise response in patients satisfying the full crite-
ria for HPS. Fourth, there is now clinical evidence for the existence of a cirrhotic cardiomyopathy. Because we did not directly measure cardiac output during exercise, it is possible that exercise limitation in HPS patients resulted, in part, from a subnormal increase in exercise stroke volume. The peak \( \text{VO}_2/\text{HR} \) (an indirect measure of stroke volume) was lower in the HPS patients, but this did not achieve statistical significance and may also result from decreased oxygen extraction. If a subnormal increase in cardiac output exists, it may further contribute to exercise-related hypoxemia by decreasing the mixed venous oxygen content. Lastly, we were unable to restudy our patients on supplemental oxygen to determine how correction of exercise-induced hypoxemia impacts on peak \( \text{VO}_2 \). Interestingly, along these lines, the HC subjects developed neither exercise-related worsening in \( \text{PaO}_2 \) nor further reduction in peak \( \text{VO}_2 \) percent predicted compared with the NC subjects.

In conclusion, patients with the HPS demonstrate a significant reduction in aerobic capacity when compared with cirrhotics without the syndrome. This abnormal response is characterized by significant hypoxemia with widening of the A-a \( \text{O}_2 \) gradient, early onset of the ventilatory threshold, and elevated dead space at peak exercise. These findings support the concept that an abnormal pulmonary circulation contributes, in part, to exercise limitation in cirrhotics with HPS.

REFERENCES